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10/787,421	02/26/2004	Majed M. Hamawy	960296.99187	5432

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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
06/27/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

pat-dept@quarles.com

Office Action Summary	Application No.	Applicant(s)	
	10/787,421	HAMAWY, MAJED M.	
	Examiner	Art Unit	
	NORA M. ROONEY	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,9 and 14-17* is/are pending in the application.

4a) Of the above claim(s) *14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 9 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/03/2008 has been entered.

2. Claims 2, 9 and 14-17 are pending.

3. Claims 14-16 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/02/2006.

4. Claims 2, 9 and 17 are currently under examination as they read on a method for monitoring whether an animal is experiencing kidney transplant rejection by detecting the protein of SEQ ID NO:1 in a kidney tissue sample.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 2, 9 and 17 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: a method of monitoring whether an animal that has received a transplanted kidney is experiencing kidney transplant rejection, the method comprising: analyzing a sample of the kidney of the animal for the presence of a marker protein selected from the group consisting of: (a) phosphorylated protein which is SEQ ID NO:1 in a form comprising phosphorylated tyrosine wherein the analyzing comprises: contacting the sample or a homogenate thereof with **a labeled antibody that specifically binds to SEQ ID NO:1 and an anti-phosphotyrosine antibody**; and (b) protein which is SEQ: ID NO. 1; wherein the analyzing comprises: contacting the sample or a homogenate thereof with **a labeled antibody that specifically binds to SEQ ID NO:1**; detecting the extent to which labeled antibody becomes bound to the marker protein or said fragment of the phosphorylated marker protein as a result thereof; and either: (i) comparing the amount of marker protein bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such marker protein is thereby detected in the sample, or if the amount of marker protein thereby detected in the sample is below a known standard level, such a result would be indicative of kidney transplant rejection; or (ii) comparing the amount of said fragment of the phosphorylated marker protein bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such fragment o the phosphorylated marker protein bound to the labeled antibody is thereby detected, or if the

amount of such fragment of the phosphorylated marker protein bound to the labeled antibody thereby detected is below a known standard level, such a result would be indicative of kidney transplant rejection; wherein the animal is a primate; and wherein the animal is a human; does not reasonably provide enablement for: a method of monitoring whether an animal that has received a transplanted kidney is experiencing kidney transplant rejection, the method comprising: analyzing a sample of the kidney of the animal for the presence of a marker protein selected from the group consisting of: (a) phosphorylated protein which is SEQ:ID NO. 1 in a form comprising phosphorylated tyrosine; and (b) protein which is SEQ: ID NO. 1; **wherein the analyzing comprises: contacting the sample or a homogenate thereof with a labeled antibody capable of binding to the marker protein in the sample or to a fragment of the phosphorylated marker protein in the homogenate that is about 55kDa in size,** detecting the extent to which labeled antibody becomes bound to the marker protein or said fragment of the phosphorylated marker protein as a result thereof; and either: (i) comparing the amount of marker protein bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such marker protein is thereby detected in the sample, or if the amount of marker protein thereby detected in the sample is below a known standard level, such a result would be indicative of kidney transplant rejection; or (ii) comparing the amount of said fragment of the phosphorylated marker protein bound to the labeled antibody to a known standard to diagnose whether the animal is experiencing kidney transplant rejection, whereby the method is conducted such that if no such fragment o the phosphorylated marker protein bound to the labeled antibody is thereby detected, or if the amount of such fragment of the phosphorylated marker protein

bound to the labeled antibody thereby detected is below a known standard level, such a result would be indicative of kidney transplant rejection of claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons as set forth in the Office action mailed on 12/03/2007.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

On pages 8-12, the specification discloses:

1.) Rat kidney homogenates were subjected to a series of 30, 50, and 100 kd cut-off filters and SDS-PAGE 2- dimensional gel electrophoresis before being transferred to a membrane and immunoblotted with antiphosphotyrosine antibody. A phosphorylated protein band excised from the gel was analyzed by mass spectrometry and determined to contain phosphorylated selenium-binding protein;

2.) Baboon kidneys homogenates were subjected to two-dimensional electrophoresis (IEF and SDS-PAGE) and the gels were then either stained with Coomassic blue or silver staining or transferred to PVDF membranes and with anti- phosphotyrosine antibodies;

3.) Rhesus monkey tissue lysates were subjected to 2-D electrophoresis, transferred to a membrane and immunoblotted with anti-phosphotyrosine antibodies. A phosphorylated fifty kDa protein band was identified by mass spectrometry as containing phosphorylated SBP-1;

4.) Rhesus kidney lysates were subjected to a series of 100 and 50 kDa cut-off filters, 2-D electrophoresis and Western transfer before the proteins immunoblotted were with anti-SBP-I Ab. The anti-SBP-1 antibody was then stripped off and the membranes were re-immunoblotted with anti- phosphotyrosine antibody which detected identical spots; and

5.) Rhesus monkey kidney tissue samples were subjected to 2-D gel electrophoresis before being transferred to a membrane and immunolabeled with anti-SBP-1 antibodies.

The specification has disclosed a series of experiments whereby kidney homogenates are filtered, separated by gel electrophoresis and immunoblotted with anti-phosphotyrosine antibody to reveal bands, particularly one around 55kDa, which were determined by mass spectrometry or immunoblotting with anti-SBP-1 to contain phosphorylated SBP-1 or fragments thereof. The specification also discloses a method whereby SBP-1 (SEQ ID NO:1) is detected after electrophoresis using anti-SBP-1 antibody. However, the recited claims encompass determining the rejection status of an animal by detecting the presence of phosphorylated SBP-1 using anti-phosphotyrosine antibodies alone, though the method is not enabled for determining the presence of phosphorylated SBP-1 using only anti-phosphotyrosine antibody as anti-phosphotyrosine antibody is not specific for SBP-1 (SEQ ID NO:1). The specification does not adequately disclose the genus of using any "labeled antibody capable of binding to the marker protein" to detect phosphorylated SBP-1 for use in the claimed method. Rather, immunoblotting a gel or a membrane with anti-phosphotyrosine antibodies will result in the visualization of any and all proteins that are phosphorylated at a tyrosine. Therefore, because of the unpredictability of the identity of the protein detected, the recited method does not accurately predict the presence of

phosphorylated SBP-1 on a gel that is immunoblotted using anti-phosphotyrosine antibodies alone.

There is no way to accurately predict the identity of a protein of any given size on a gel unless the protein is analyzed to determine its specific sequence identity by a protein-specific antibody or other methods known in the art. Even if the identity of all proteins of an actual given molecular size are known, which is not the case, the identity of all proteins and protein fragments that by a given method or under a specific set of cellular conditions are visualized on a gel as a given size is not known. Protein and protein fragment sizes vary by animal species, cellular modifications and events, gel filtration conditions and as the specification acknowledges on page 4, lines 11-14, homogenation conditions. Therefore, there is unpredictability in determining the identity of proteins and fragments based upon size determined on a gel or other laboratory procedure without confirmation of the specific identity of the protein by methods known in the art, even if all proteins of a given molecular weight were known. However, all proteins of any given molecular weight are not known, so the accuracy of the method is further reduced by the very likely possibility of detecting other proteins of the same molecular size. In particular, the art of Laminski et al. (PTO-892; Reference U) teaches that samples of baboon kidney transplants probed with anti-phosphotyrosine antibodies showed bands at 45, 55 and 66 kDa that were intensified in the presence of cAMP (In particular, page 1093, last paragraph, whole document). The Laminski reference goes on to teach that the band at 55kDa has a molecular mass that is similar to that reported for type II cyclic AMP-dependent protein kinase regulatory subunit (In particular, page 1094, last paragraph). In addition, Wade et al. (PTO-892; Reference V) teaches that UT-A2 is a 55kDa urea transporter protein found in kidneys whose

expression is regulated by vasopressin (In particular, abstract, whole document) and Gang et al. (PTO-892; Reference W) teaches that osteopontin is a phosphorylated protein of 55kDa found in the kidneys and urine (In particular, abstract, first 3 paragraphs on page 374). The art of Biber et al. (PTO-892; Reference X) compared to the art of Laminski et al. (PTO-892; Reference U) shows that the experimental procedures and animal tissues used make a difference in the outcome of the results. Biber et al. teaches that rat kidneys samples probed with anti-phosphotyrosine antibodies showed bands at 40, 46 and 55 kDa that were intensified in the presence of cAMP (In particular, page 1093, last paragraph, whole document), whereas Laminski et al. teaches that samples of baboon kidneys transplants probed with anti-phosphotyrosine antibodies showed bands at 45, 55 and 66 kDa that were intensified in the presence of cAMP (In particular, page 1093, last paragraph, whole document). Therefore, detection of a protein band of a specific molecular weight in all animals using any procedure will not generate consistent results. Because of the lack of guidance in the specification and examples and state of the art, the recited method does not accurately predict the presence of phosphorylated SBP-1 on a gel that is immunoblotted using anti-phosphotyrosine antibodies alone.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments filed on 03/03/2008 have been fully considered, but are not found persuasive.

Applicant argues:

"There is nothing of record to indicate the prominent presence in kidneys of another phosphorylated tyrosine peptide of about 55kDa. Regardless, even if the Office were to find such a teaching, it is respectfully asserted that still would not undermine enablement with respect to the amended claims.

Both the specification and the art teach how to make a specific antibody for phosphorylated SBP-1 itself. See original claim 15 and paragraph [0061] of the original specification. Further, note that the Torrealba et al. reference of record by Applicant's lab confirms the ability to generate specific antibodies.

While the specification exemplified the more general anti- phosphotyrosine antibody to detect the "about 55kDa fragment", Applicant also taught at paragraph [0023] developing specific antibodies to the fragment. Hence, Applicant has enabled specificity with respect to at least an about 55kDa fragment of phosphorylated SBP-I.

Apart *from* this, contrary to the Advisory Action's comment, with respect to the fragment homogenation is required in the claims ("..or to a fragment of the phosphorylated marker protein in the homogenate..."). Hence, apart from the fact that there is nothing of record to support a substantial presence by a conflicting phosphorylated protein fragment of "about 55kDa", whatever else in nature might hypothetically be phosphorylated tyrosine-containing and about 55kDa has been shown in experiments not to survive the homogenation in sufficient quantities to be a problem (see the declaration).

In any event, even if something else in nature had those properties, and survived the method conditions, that wouldn't create a false positive problem (or even a false negative problem). In such a case, both the comparison standard and the test would presumably have the same base level of presence of the hypothetical purported interfering peptide. In a non- rejecting patient, there would then also be the same level of the SBP-I fragment in both. In a rejecting patient, one would then still see a drop-off (albeit not complete elimination) at the about 55kDa size. The point is that even though something would remain at the 55kDa point on the gel when a patient is rejecting, it would still appear less prominent when the patient was rejecting.

Hence, even using the Office Action's assumptions, and just the more general anti-phosphotyrosine antibody, the prominent presence of the irrelevant protein wouldn't make a false positive (as presence is indicative of lack of rejection). Further, it wouldn't mask a rejection (to create a false negative) as the relative decrease (as distinguished from total absence) can still indicate rejection.

Of course, that discussion assumes that the best available antibody would be the anti-phosphotyrosine antibody. As noted above, a more specific fragment antibody per paragraph [0023] could visualize only the relevant fragment. "

It is the Examiner's position that they have provided evidence *supra* of the significant presence of phosphorylated proteins of 55kDa in homogenized kidney samples and particularly in transplanted baboon kidney samples. Applicant's argument that the presence of another phosphorylated 55kDa protein that survives homogenation would not create a false positive or

false negative problem is unpersuasive as Applicant and the Examiner are not able to determine factors that effect phosphorylation and/or expression of the reference protein undergoing transplant rejection and subjected to the recited method. The Examiner acknowledges that a false-positive, indicating that the kidney is undergoing rejection when it is not, is not as likely because rejection is associated with the lack of a band at 55kDa. However, it is possible to have a decreased band at 55kDa that is the result of changes to the reference 55kDa protein and not due to changes in the SBP-1 protein or its phosphorylation. Since the method is not directed to detecting kidney transplant rejection status based upon an absolute result, the reference protein can give a false positive result, as encompassed by the recited method. In the same way, a false negative result is possible wherein the presence of transplantation rejection increases the expression and/or phosphorylation of the reference protein while the SBP-1 decreases.

Whether or not one of ordinary skill in the art would have able to make an anti-SBP-1 antibody, the claims as recited are not enabled because they encompass the use of an anti-phosphotyrosine antibody to specifically detect phosphorylated SBP-1. The specification is directed to supporting the contention that anti-phosphotyrosine alone can be used to specifically detect phosphorylated SBP-1. However, it is the Examiner's position that anti-phosphotyrosine alone cannot be used to specifically detect phosphorylated SBP-1. Therefore, the specification does not adequately disclose the genus of using any "labeled antibody capable of binding to the marker protein" for use in the claimed method. Because of the unpredictability in the method discussed *supra*, one of ordinary skill in the art would be required to perform undue experimentation to practice the claimed invention commensurate in scope with the claims.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

June 18, 2008

Nora M. Rooney

Patent Examiner

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